

IN THE CLAIMS:

We claim:

1. (Currently Amended) A method of isolating a polynucleotide of a microbe or pathogen that is expressed only *in vivo* comprising ~~the steps of:~~
 - (a) obtaining an antibody sample from one or more hosts infected with the microbe or pathogen;
 - (b) ~~adsorbing the antibody sample antibodies against antigens that are expressed by the microbe *in vivo* and *in vitro*~~ with cells or cellular extracts of the microbe or pathogen that have been grown *in vitro*;
 - (b) (c) isolating unadsorbed antibodies; and
 - (c) (d) probing an expression library of clones of the ~~microbe's~~ microbe or pathogen DNA or RNA with the unadsorbed antibodies of ~~step (b)~~ (c) and isolating clones from the expression library to which the unadsorbed that bind to the antibodies bind of step (b);
wherein a polynucleotide of the microbe or pathogen that is expressed only *in vivo* is isolated.
2. (Currently Amended) The method of claim 1 wherein the polynucleotide of the microbe or pathogen that is expressed only *in vivo* encodes an *in vivo* induced antigen.
3. (Previously Presented) The method of claim 2 wherein the *in vivo* induced antigen is capable of eliciting an immune response in an animal.
4. (Previously Presented) The method of claim 3 wherein the animal is selected from the group consisting of humans, baboons, chimpanzees, macaques, cattle, sheep, pigs, horses, goats, dogs, cats, rabbits, guinea pigs, rats, mice, chickens, ducks, and fish.
5. (Original) The method of claim 1 further comprising the step of determining the nucleic acid sequence of the polynucleotide.
6. (Currently Amended) A method of confirming the isolated polynucleotide of claim 1 as expressed only *in vivo* comprising ~~the steps of:~~

- (a) expressing and isolating a polypeptide from the isolated polynucleotide of claim 1;
- (b) producing antibodies to the polypeptide; and
- (c) demonstrating that the antibodies are reactive with ~~probing~~ biological samples from disease sites from a host infected with ~~or previously infected with~~ the microbe ~~or pathogen~~, with the antibodies of step (b), but not reactive with cells or cellular extracts of the microbe or pathogen that have been grown *in vitro*;

whereby the isolated polynucleotide is confirmed as being expressed only *in vivo*.

7. (Currently Amended) The method of claim 1 wherein the ~~antibodies~~ antibody ~~sample of step (a) are is obtained from~~ sera from the one or more hosts infected with, ~~or previously infected with~~ the microbe ~~or pathogen~~.
8. (Currently Amended) The method of claim 1 wherein the microbe ~~or pathogen~~ is selected from the group consisting of a bacterium, a virus, a parasite, a prion, and a fungus.
9. (Currently Amended) The method of claim 1 wherein the microbe ~~or pathogen~~ is selected from the group consisting of *Candida*, *Aspergillus*, *Sporothrix*, *Blastomyces*, *Histoplasma*, *Cryptococcus*, *Pneumocystis*, *Coccidioides*, *Tinea*, *Toxoplasma*, *Plasmodium*, *Pseudomonas*, *Actinobacillus*, *Staphylococcus*, *Bacillus*, *Clostridium*, *Listeria*, *Corynebacterium*, *Actinomyces*, *Mycoplasma*, *Nocardia*, *Bordetella*, *Brucella*, *Francisella*, *Legionella*, *Enterobacter*, *Escherichia*, *Klebsiella*, *Proteus*, *Salmonella*, *Shigella*, *Streptococcus*, *Yersinia*, *Vibrio*, *Campylobacter*, *Helicobacter*, *Bacteroides*, *Chlamydia*, *Borrelia*, *Treponema*, *Leptospira*, *Aeromonas*, *Rickettsia*, *Ascaris*, *Cryptosporidium*, *Cyclospora*, *Entamoeba*, *Giardia*, *Shistosoma*, *Trypanosoma*, herpes virus, cytomegalovirus, Epstein-Barr virus, hepatitis virus, adenovirus, papillomavirus, polyomavirus, enterovirus, rotavirus, influenza virus, paramyxovirus, rubella virus, rhabdovirus, human immunodeficiency virus, arenavirus, rhinovirus, and reovirus.

10. (Previously Presented) The method of claim 7, wherein the one or more hosts are an animal selected from the group consisting of humans, baboons, chimpanzees, macaques, cattle, sheep, pigs, horses, goats, dogs, cats, rabbits, guinea pigs, rats, mice, chickens, ducks, and fish.
11. (Currently Amended) A method of comparing polynucleotides of a microbe or pathogen that are expressed only *in vivo* and at different stages of infection of the microbe or pathogen comprising the steps of:
- (a) obtaining a first antibody sample from one or more hosts infected with the microbe or pathogen, wherein each host is in about the same stage of the infection;
 - (b) adsorbing a the first sera antibody sample from one or more hosts infected with or previously infected with the microbe, with cells or cellular extracts of the microbe or pathogen that have been grown *in vitro*, ~~wherein each host is in about the same stage of the infection;~~
 - (c) obtaining a second antibody sample from one or more hosts infected with the microbe or pathogen, wherein each host is in about the same stage of the infection, wherein the stage of the infection is different from the stage of infection in step (a);
 - (~~b~~) (d) adsorbing a the second sera antibody sample from one or more hosts infected with or previously infected with the microbe, with cells or cellular extracts of the microbe or pathogen that have been grown *in vitro*, ~~wherein each host is in about the same stage of the infection, wherein the stage of the infection is different from the stage of infection in step (a);~~
 - (~~c~~) (e) isolating unadsorbed antibodies from the first antibody sample and from the second serum antibody sample;
 - (~~d~~) (f) probing a first expression library of clones of the microbe or pathogen with the unadsorbed antibodies from the first serum antibody sample and isolating clones from the first expression library to which the unadsorbed that bind to antibodies bind from the first serum sample, and probing a second expression library of clones of the microbe or pathogen with the unadsorbed antibodies from the second serum antibody sample and isolating clones from the second

expression library ~~to which the unadsorbed that bind to~~ antibodies ~~bind from the second serum sample~~, wherein polynucleotides of the microbe ~~or pathogen~~ that are expressed only *in vivo* are isolated for the first and second ~~serum antibody~~ sample; and

~~(e)~~ (g) comparing the polynucleotides of the microbe ~~or pathogen~~ that are expressed only *in vivo* and at different stages of infection of the microbe ~~or pathogen~~.

12. (Original) The method of claim 11 wherein the first expression library and the second expression library are the same expression library.
13. (Currently Amended) A method of comparing polynucleotides of a microbe ~~or pathogen~~ that are expressed only *in vivo*, wherein the microbe ~~or pathogen~~ has infected its host by different routes of infection comprising the steps of:
 - (a) obtaining a first antibody sample from one or more hosts infected with the microbe or pathogen, wherein each host has been infected by about the same route of infection;
 - ~~(b) adsorbing a the first sera antibody sample from one or more hosts infected with or previously infected with the microbe, with cells or cellular extracts of the microbe or pathogen that have been grown in vitro, wherein each host has been infected by about the same route of infection;~~
 - (c) obtaining a second antibody sample from one or more hosts infected with the microbe or pathogen, wherein each host has been infected by about the same route of infection, wherein the route of infection is different from the route of infection in step (a);
 - ~~(b) (d) adsorbing a the second sera antibody sample from one or more hosts infected with or previously infected with the microbe, with cells or cellular extracts of the microbe or pathogen that have been grown in vitro, wherein each host has been infected by about the same route of infection, wherein the route of infection is different from the route of infection in step (a);~~
 - ~~(e)~~ (c) isolating unadsorbed antibodies from the first ~~serum antibody~~ sample and from the second ~~serum antibody~~ sample;

- (~~d~~) (f) probing a first expression library of clones of the microbe or pathogen with the unadsorbed antibodies from the first serum antibody sample and isolating clones from the first expression library to which the unadsorbed antibodies bind from the first serum sample, and probing a second expression library of clones of the microbe or pathogen with the unadsorbed antibodies from the second serum antibody sample and isolating clones from the second expression library to which the unadsorbed antibodies bind from the second serum sample, wherein polynucleotides of the microbe or pathogen that are expressed *in vivo* are isolated for the first and second serum antibody sample; and
- (~~e~~) (g) comparing the polynucleotides of the microbe or pathogen that are expressed only *in vivo* by different routes of infection of the microbe or pathogen.
14. (Original) The method of claim 13 wherein the first expression library and the second expression library are the same expression library.
15. (Currently Amended) A method of confirming an animal model of microbial infection as a valid model comprising the steps of:
- (a) obtaining a first antibody sample from one or more first animal model hosts infected with a microbe or pathogen;
- (~~b~~) adsorbing a the first sera antibody sample from one or more animal model hosts infected with or previously infected with a microbe, with cells or cellular extracts of the microbe or pathogen that have been grown *in vitro*;
- (c) obtaining a second antibody sample from one or more second hosts infected with the microbe or pathogen, wherein the second host is a different species of animal than the first animal model host;
- (~~b~~) (d) adsorbing a the second sera antibody sample from one or more second hosts infected with or previously infected with the microbe, with cells or cellular extracts of the microbe or pathogen that have been grown *in vitro*; wherein the second host is a different species of animal than the animal model host;
- (~~e~~) (e) isolating unadsorbed antibodies from the first serum antibody sample and from the second sera antibody sample;

- (d) (f) probing a first expression library of clones of the microbe or pathogen with the unadsorbed antibodies from the first sera antibody sample and isolating clones from the first expression library to which the unadsorbed ~~that bind to~~ antibodies bind from the first sera sample, and probing a second expression library of clones of the microbe or pathogen with the unadsorbed antibodies from the second sera antibody sample and isolating clones from the second expression library to which the unadsorbed ~~that bind to~~ antibodies bind from the second sera sample, wherein polynucleotides of the microbe or pathogen that are expressed only *in vivo* are isolated for the first and second sera antibody sample; and
- (e) (g) comparing the polynucleotides of the microbe or pathogen that are expressed only *in vivo* in the first animal model host and the second host; wherein if the polynucleotides expressed only *in vivo* in the first animal model and in the second host are the same or similar, then the first animal model is confirmed as a valid model.
16. (Original) The method of claim 15 wherein the first expression library and the second expression library are the same expression library.
17. (Currently Amended) The method of claim 15 wherein the first animal model host and the second host are selected from the group consisting of humans, baboons, chimpanzees, macaques, cattle, sheep, pigs, horses, goats, dogs, cats, rabbits, guinea pigs, rats, mice, chickens, ducks, and fish.
18. (New) A method of isolating a vaccine target for a particular microbe or pathogen comprising:
- (a) obtaining an antibody sample from one or more hosts infected with the microbe or pathogen;
 - (b) adsorbing the antibody sample with cells or cellular extracts of the microbe or pathogen that have been grown *in vitro*;
 - (c) isolating unadsorbed antibodies; and
 - (d) probing an expression library of clones of the microbe or pathogen with the unadsorbed antibodies of (c) and isolating clones from the expression library to which the unadsorbed antibodies bind;
- wherein a vaccine target for the particular microbe or pathogen is isolated.

19. (New) A method of identifying a diagnostic target for a particular microbe or pathogen comprising:
- (a) obtaining an antibody sample from one or more hosts infected with the microbe or pathogen;
 - (b) adsorbing the antibody sample with cells or cellular extracts of the microbe or pathogen that have been grown *in vitro*;
 - (c) isolating unadsorbed antibodies; and
 - (d) probing an expression library of clones of the microbe or pathogen with the unadsorbed antibodies of (c) and isolating clones from the expression library to which the unadsorbed antibodies bind;
- wherein a diagnostic target for the particular microbe or pathogen is isolated.